131. A nucleic acid sequence capable of hybridizing to the nucleic acid sequence of claim 122, wherein said nucleic acid sequence encodes a protein recognized by T cells specific for *Cry j* II.

132. A nucleic acid sequence encoding a protein or peptide having a high degree of homology with a protein allergen or a peptide of *Cry j* I.

133. The nucleic acid sequence of claim 132 having at least 50% homology with the nucleic acid sequence of *Cry j* I as shown in SEQ ID NO:1.

134. A nucleic acid sequence encoding a protein or peptide having a high degree of homology with a protein allergen or a peptide of *Cry j* II.

135. The nucleic acid sequence of claim 134 having at least 50% homology with the nucleic acid sequence of *Cry j* II as shown in SEQ ID NO:133.

136. The nucleic acid sequence of claim 134 having at least 90% homology with the nucleic acid sequence of *Cry j* II as shown in SEQ ID NO:133.

137. The nucleic acid sequence of claim 132 having at least 90% homology with the nucleic acid sequence of *Cry j* I as shown in SEQ ID NO:1.

Remarks

Claims 1-3 were amended to specifically refer to the nucleic acid sequence of *Cry j* I as shown in SEQ ID NO:1 and *Cry j* II as shown in SEQ ID NO:133. Support for "degeneracy" can be found at page 11, lines 25-34. Support for the term "antigenic" in amended claims 4 and 5 can be found in the specification page 15, lines 6-37. Support for amended claim 7 can be found in the specification page 12, line 19 through page 13,

line 28. Claim 61 was amended to include the limitations from canceled claim 56 to which it refers.

Support for new claims 126-131 can be found at page 9, line 35 through page 10, line 1, and at page 11, lines 4-14.

Support for new claims 132-137 can be found at page 10, lines 16-27, and at page 10, line 34 through page 11, line 3.

Pending claims were amended and new claims were added to more clearly define Applicants' invention. Support for all amendments and new claims can be found in the specification; no new matter is added.

Election/Restriction

Applicants respectfully request that the Examiner reconsider the restriction imposed (Paper No. 8) between nucleic acid sequences for *Cry j* I and *Cry j* II (Groups I and IX). As stated in Applicants' Amendment And Response To Restriction Requirement, Applicants submit that *Cry j* I and *Cry j* II should be treated as two species covered in a generic claim 1 (as amended). Claim 1, as amended, provides an allowable generic claim that encompasses the previously claimed species.

35 U.S.C. §121 states that if two or more independent and distinct inventions are claimed in one application, the Commissioner may require the application to be restricted to one of the inventions. Applicants respectfully submit that the subject matter of Groups I and IX from the Examiner's restriction requirement are related and dependent, and therefore the restriction requirement is improper. Moreover, since both Group I (*Cry j* I) and Group IX (*Cry j* II) are classified in Class 435, subclass 69.3, there is no additional

burden placed on the Examiner. Applicants respectfully request that pending claims 1, 4, 7, 12 and 40 be examined as generic claims covering species *Cry j* I and *Cry j* II.

35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-12, 40 and 61 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim Applicants' invention. Applicants respectfully traverse this rejection.

The Examiner rejected Claims 1, 6 and 12 on the basis that the metes of the subject matter were not clear. Claim 1, as amended (and claims 6 and 12, which depend upon claim 1), includes a reference to SEQ ID NO:1 which gives the nucleic acid sequence for *Cry j* I discovered by Applicants, and SEQ ID NO:133 which gives the nucleic acid sequence for *Cry j* II discovered by Applicants. The metes of the claims are clear in that they relate to a specific nucleotide sequence as taught by Applicants. Applicants respectfully request that the rejection of Claims 1, 6 and 12 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim 5 was rejected under 35 U.S.C. 112, second paragraph, "for use of the term 'consists essentially' since said term is not used to define the metes and bounds of a claimed compound." Claim 5 has been amended to delete the phrase "consists essentially". Applicants respectfully request that the rejection of Claim 5 under 35 U.S.C. §112, second paragraph, be withdrawn.

Claim 61 was rejected because it referred to a withdrawn claim. Applicants have amended Claim 61 to include the limitations of the withdrawn claim upon which it

depends. Applicants respectfully request that the rejection of Claim 61 under 35 U.S.C. §112, second paragraph, be withdrawn.

35 U.S.C. §112, First Paragraph

The Examiner rejected Claims 1-12, 40 and 61 under 35 U.S.C. §112, first paragraph, alleging the absence of an enabling disclosure. Applicants respectfully traverse this rejection.

If one of ordinary skill in the art can construct the claimed invention following the teachings of the specification, then enablement has been shown. The enablement requirement is measured with respect to one skilled in the art and not with respect to the general public. W.L. Gore & Assoc. v. Garlock, Inc., 721 F.2d 1540, 1556, 220 U.S.P.Q. 303, 315 (Fed. Cir. 1983). That person of ordinary skill in the art is presumed to have knowledge of all references that are sufficiently related to one another and to the pertinent art, In re Sernaker, 702 F.2d 989, 994, 217 U.S.P.Q. 1, 5 (Fed. Cir. 1983), and to have knowledge of all art reasonably pertinent to the particular problem with which the inventor was involved, Custom Accessories, Inc. v. Jeffrey-Allen Indus., Inc., 807 F.2d 955, 962, 1 U.S.P.Q.2d 1196, 1201 (Fed. Cir. 1986). As outlined in detail below, all pending claims in this case are enabled in Applicants' specification.

Specifically, the Examiner asserts that "[t]he specification provides insufficient guidance to a nucleic acid coding for the Cry j I species as broadly claimed which encompass modifications (i.e., deletions, additions, functional equivalents, or fragments)." Applicants submit that the claims, as amended, are enabled and one skilled in the art would be able to practice the claimed invention.

Claims 1-3 claim a nucleic acid sequence coding for the Japanese cedar pollen protein *Cry j* I or *Cry j* II, and give a specific nucleotide sequence in SEQ ID NO:1 and SEQ ID NO:133, respectively. There is no experimentation required to determine the sequence of the Japanese cedar pollen protein *Cry j* I or *Cry j* II (one must merely read SEQ ID NO:1 or SEQ ID NO:133), or to determine the complement sequence of that which is given in SEQ ID NO:1 or SEQ ID NO:133. Moreover, one with very little skill in the art knows that the nucleic acid sequence for a protein is subject to degeneracy (i.e., certain nucleotides may be substituted with others and not effect the final protein). For example, one could easily change a CGG codon to a CGA codon in a given sequence and still end up with arginine. (See specification page 11, lines 25-34). Applicants respectfully submit that Claims 1-3 are enabled and request that the rejection of Claims 1-3 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 4 and 5, as amended, claim antigenic fragments of *Cry j* I or *Cry j* II encoded by fragments of the nucleotide sequences of Claims 1 and 2. As taught in Applicants' specification, "antigenic fragments" refer to any "fragment of *Cry j* I which induces an immune response." (Specification page 15, lines 6-7). To determine which fragments of the *Cry j* I protein are antigenic, "[t]he allergen [*Cry j* I or *Cry j* II] may be arbitrarily divided into fragments of a desired length with no overlap of the peptides, or preferably divided into overlapping fragments of a desired length. The fragments are tested to determine their antigenicity (e.g., the ability of the fragments to induce an immune response)." (Specification page 15, lines 22-25).

Determining antigenicity of a fragment or peptide is also taught in the specification. For example, Applicants state:

Screening peptides of *Cry j* I or *Cry j* II as described herein can be accomplished using one or more of several different assays. For example, *in vitro*, *Cry j* I or *Cry j* II T cell stimulatory activity is assayed by contacting a protein or peptide known or suspected to be from *Cry j* I or *Cry j* II with an antigen presenting cell which presents appropriate MHC molecules in a T cell culture. Presentation of a peptide of *Cry j* I or *Cry j* II in association with appropriate MHC molecules to T cells in conjunction with the necessary costimulation has the effect of transmitting a signal to the T cell that induces the production of increased levels of cytokines, particularly of interleukin-2 and interleukin-4. The culture supernatant can be obtained and assayed for interleukin-2 or other known cytokines. For example, any one of several conventional assays for interleukin-2 can be employed, such as the assay described in *Proc. Natl. Acad. Sci USA*, **86**:1333 (1989) the pertinent portions of which are incorporated herein by reference. A kit for an assay for the production of interferon is also available from Genzyme Corporation (Cambridge, MA).

A common assay for T cell proliferation entails measuring tritiated thymidine incorporation. The proliferation of T cells can be measured *in vitro* by determining the amount of ^{3}H-labeled thymidine incorporated into the replicating DNA of cultured cells. Therefore, the rate of DNA synthesis and, in turn, the rate of cell division can be quantified.

In another embodiment, a *Cry j* I or *Cry j* II peptide is screened for the ability to reduce T cell responsiveness. The ability of a peptide known to stimulate T cells, to inhibit or completely block the activity of purified native *Cry j* I or *Cry j* II or portion thereof and induce a state of T cell nonresponsiveness or reduced T cell responsiveness, can be determined using subsequent attempts at stimulation of the T cells with antigen presenting cells that present native *Cry j* I or *Cry j* II following exposure to a *Cry j* I or *Cry j* II peptide activity. If the T cells are unresponsive to the subsequent activation attempts, as determined by interleukin-2 synthesis and T cell proliferation, a state of nonresponsiveness has been induced. See, e.g., Gimmi, et al. (1993) *Proc. Natl. Acad. Sci USA*, **90**:6586-6590; and Schwartz (1990) *Science*, **248**:1349-1356, for assay systems that can be used as the basis for an assay in accordance with the present invention.

(Specification page 16 line 21 through page 17, line 11). Additionally, Applicants, at page 31, lines 16-25, teach the following:

In order to determine precise T cell epitopes by, for example, fine mapping techniques, a peptide having T cell stimulating activity and thus comprising at least one T cell epitope as determined by T cell biology techniques is modified by addition or deletion of amino acid residues at either the amino or carboxy terminus of the peptide and tested to determine a change in T cell reactivity to the modified peptide. If two or more peptides which share an area of overlap in the native protein sequence are found to have human T cell stimulating activity, as

> determined by T cell biology techniques, additional peptides can be produced comprising all or a portion of such peptides and these additional peptides can be tested by a similar procedure. Following this technique, peptides are selected and produced recombinantly or synthetically. Example 11 discusses preferred peptides of the invention produced in accordance with these techniques.

Applicants clearly teach one skilled in the art how to practice the invention of Claims 4 and 5. Indeed, the Examiner admits that the specification does disclose "peptides of *Cry j* I that have T cell stimulating activity." (Page 5, lines 6-7 of Office Action). Applicants certainly are entitled to claim the nucleic acid sequences for such peptides. Applicants respectfully request that the rejection of Claims 4 and 5 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 6-12, 40 and new Claims 123 and 125 all relate to expression vectors and host cells comprising the nucleic acid sequences of Claims 1-3. These claims, following the specification (page 12 line 19 through page 13 line 37) and techniques known in the art, are enabled to one of skill in the art. Applicants respectfully request that the rejection of Claims 6-12 and 40 under 35 U.S.C. §112, first paragraph, be withdrawn.

Finally, Claim 61, as amended to include specific amino acid sequences, is enabled by Applicants specification. The nucleotide sequences claimed in Claim 61 are evident from the amino acid sequences spelled out in the claims. The phrase "functional equivalent" used in Claim 61 is explained and taught in the specification at page 9, line 35 through page 10, line 15, and at page 11, lines 25-34. For example, Applicants state:

> An equivalent of an oligonucleotide sequence is one which is 1) a sequence capable of hybridizing to a complementary oligonucleotide to which the sequence (or corresponding sequence portions) of SEQ ID NO: 1 or SEQ. ID. NO.: 133 or fragments thereof hybridizes, or 2) the sequence (or corresponding sequence portion) complementary to SEQ ID NO: 1, or SEQ. ID. NO.: 133 and/or 3) a sequence which encodes a product (e.g., a polypeptide or peptide) having the

same functional characteristics of the product encoded by the sequence (or corresponding sequence portion) of SEQ ID NO: 1 or SEQ. ID. NO: 133. Whether an equivalent of a nucleic acid must meet one or both criteria will depend on its use (e.g., if it is to be used only as an oligoprobe, it need meet only the first or second criteria and if it is to be used to produce a *Cry j* I or *Cry j* II, it need only meet the third criterion).

As used herein, the functional equivalent of a peptide includes peptides having the same or enhanced ability to bind MHC; peptides capable of stimulating the same T cell subpopulations; peptides having the same or increased ability to induce T cell responses such as stimulation (proliferation or cytokine secretion), peptides having the same or increased ability to induce T cell non-responsiveness or reduced responsiveness, peptides having reduced IgE binding, and peptides which elicit minimal IgE synthesis stimulating activity. Minimal IgE stimulating activity refers to IgE synthesis stimulating activity that is less than the amount of IgE production elicited by purified native *Cry j* I, *Cry j* II, *Jun s* I or *Jun v* I.

* * *

Isolated nucleic acids encoding a *Cry j* I or *Cry j* II peptide, as described herein, and having a sequence that differs from the nucleotide sequence shown in Fig. 4a-b (SEQ ID NO: 1) or Fig. 28 (SEQ ID NO: 133) due to degeneracy in the genetic code are also within the scope of the invention. Such nucleic acids encode functionally equivalent protein or peptides (i.e., protein or peptides having at least a portion of the activity of *Cry j* I or *Cry j* II) but differ in sequence from the nucleic acid sequence of Fig. 4a-b (SEQ ID NO: 1) or Fig. 28 (SEQ ID NO: 133) due to the fact that a number of naturally-occurring amino acids are encoded by more than one nucleotide triplet. Codons that specify the same amino acid, or synonyms (for example, CAU and CAC are synonyms for histidine) may result in "silent" mutations which do not affect the amino acid sequence of the *Cry j* I or *Cry j* II protein. However, it is expected that DNA sequence polymorphisms that do lead to changes in the amino acid sequence of *Cry j* I or *Cry j* II will exist within Japanese cedar pollen.

Applicants respectfully request that the rejection of Claim 61 under 35 U.S.C. §112, first paragraph, be withdrawn.

Applicants are confused as to the Examiner's reference to "fragments that modify B cell responses", "fragments that bind IgE but do not result in mediator release", and "modifications to *Cry j* I [which] would result in the reduction of an allergic response

following the administration of the modified *Cry j* I." (Page 5, lines 9-15 of Office Action). Applicants submit that these are limitations in claims that have been withdrawn from consideration in this case (See, e.g., withdrawn Claims 48, 62-64). Applicants submit that it is improper for the Examiner to read the limitations of these withdrawn claims onto the pending claims in this case. Applicants respectfully request that the rejection of Claims 1-12, 40 and 61 under 35 U.S.C. 112, first paragraph, be withdrawn.

The Examiner has also stated that an undue amount of experimentation would be required by one skilled in the art to determine "antigenic fragments." Applicants disagree. That some experimentation is required does not preclude finding an enabling disclosure. DeGeorge v. Bernier, 226 U.S.P.Q. 758, 762 (Fed. Cir. 1985). Only a finding that the amount of experimentation is "unduly extensive" warrants a corresponding finding that the disclosure is not enabling. Id. The key word is "undue," not "experimentation." In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the specification of the present application is enabled and would teach one of ordinary skill in the art, with presumed knowledge of all relevant references, how to practice the present invention without undue experimentation. Applicants' disclosure "provides considerable direction and guidance on how to practice their invention and presents working examples. There was a high level of skill in the art at the time when the application was filed, and all of the methods needed to practice the invention were well known." Wands, 8 U.S.P.Q.2d at 1406; PPG Industries Inc. v. Guardian Industries Corp., 37 U.S.P.Q.2d 1618, 1623-1624 (Fed. Cir. 1996). Therefore,

Applicants respectfully request that the Examiner's rejection of Claims 1-12, 40 and 61 under 35 U.S.C. §112, first paragraph, be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the instant application is in condition for allowance. Favorable action by the Examiner is earnestly solicited. The Examiner is invited to call Applicants attorney at the telephone number below to expedite allowance of the pending claims.

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